President's Message

Dear Fellow DDTSS members:

Greetings from sweltering Indianapolis; it seems as if it was just yesterday we were dealing with snow and ice! Likewise, it seems we have just returned from the SOT Annual Meeting in Washington, DC, yet nearly 4 months have passed and the officers of DDTSS have completed several projects during the intervening period.

To briefly bring everyone up to date, let me begin with a recap of key events from the 2011 SOT meeting. First, we had a tremendous response to our Emil A. Pfitzer graduate student and postdoctoral award competition. There are more details following in the newsletter so I won't spill the beans here but, on behalf of the officers, I did want to thank all participants and their mentors for submitting their high quality research for review by the officers. This year, we also had judging performed by individuals outside the officers group and thus I wish to acknowledge and thank the following DDTSS members for responding to our request to the general membership to serve as judges: **Ravi Dugyala, Eric Harstad, Vic Kadambi, Mike McKenna** and **Holly Skaggs**, as well as newly elected Councilor **Stefan Ruepp**. This represents one example of member engagement and communication across, and amongst, the diverse training and affiliations of DDTSS members……but more on that thought in just a bit. At the reception, which was on Wednesday evening of a very busy week for everyone, we recognized the Pfitzer award winners, as well as our new officers who were elected to their positions as follows: **Yvonne Will** (Pfizer), VP-Elect; **Donna Mendrick** (FDA/NCTR), Secretary/ Treasurer; **Stefan Ruepp** (BMS), Councilor. Those who have completed their terms and are to be acknowledged for their service are **John W. Davis**, Past President (after serving in one capacity or another for 7 years!), **Melissa Rhodes**, Secretary/Treasurer, **Dan Kemp**, Councilor, **Arun Asaithambi**, Graduate Student Rep and **Kim Henderson**, Postdoctoral Rep (to learn who are the new Graduate Student and Postdoc Reps, please see the section on our Pfitzer award winners).

Second, since the SOT meeting, the officers have reviewed and ranked the 2012 meeting proposals for which the DDTSS was requested to serve as Sponsor (n=7) or Endorser (n=17). Several proposals were submitted by members of the DDTSS so we are hopeful that the science

emanating from, and or recommended by, our SS will be selected to be presented in San Francisco. Our other task, at the request of Jon Cook - SOT President, was to review and comment on two vision papers relevant to drug discovery and diagnostics that resulted from several committees convened to identify the most promising scientific opportunities of the next decade for The Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Finally, to come back to my aforementioned topic of engagement and communication - This is YOUR SPECIALTY SECTION, we are 384 members strong! We are employed in varying sectors including industry, government, and academia. Accordingly, we all have different likes and dislikes and different priorities. Yet, we are all members of DDTSS. During my year as President, I would like to hear from you; I'd like to know why you belong to DDTSS (at $15 I know it's inexpensive but hopefully it's more than that), I'd like to know what you'd like to get out of DDTSS membership and how you'd like to contribute to achieve those goals. At a recent conference on the west coast, I was very pleased when DDTSS member Martin Dyroff (Astra Zeneca) came up to me to discuss various aspects of the DDTSS. I know that my fellow officers share this same vision of engagement and communication. Thus, please don't hesitate to e-mail me (cthomas@lilly.com) at any time, and we also plan to put together a simple survey that I hope you will respond to. As with any survey, the free text comments you submit are likely to be amongst the most impactful and actionable items resulting from the survey, so please watch for that in the future. In the meantime, please read through the rest of the newsletter, enjoy your summer and I look forward to representing and engaging with many of you over the next year!

Best regards,

Craig Thomas

Thanks to our outgoing officers (Arun Asaithambi, John Davis and Melissa Rhodes).

Cindy Afshari hands off the Presidency to Craig Thomas.

Welcome to our new officers! Stefan Ruepp, Yvonne Will and Donna Mendrick.

2011-2012 Officers Listing

President:
Craig E. Thomas cthomas@lilly.com

Vice President:
John A. Wisler jwisler@amgen.com

Vice President-Elect:
Yvonne Will - *Newly elected*
yvonne.will@pfizer.com

Secretary/Treasurer:
Donna L. Mendrick - *Newly elected*
donna.mendrick@fda.hhs.gov

Past President:
Cynthia A. Afshari cafshari@amgen.com

Councilor:
Michael A. Breider mbreider@celgene.com

Councilor:
Stefan U. Ruepp - *Newly elected*
stefan.ruepp@bms.com

Postdoctoral Representative:
Li Zhan - *Newly elected*
li.zhan@louisville.edu

Student Representative:
Rachel Tanos - *Newly elected*
racheltanos@gmail.com

Emil Pfitzer Fund

We want our members to be aware of the Emil A. Pfitzer Endowment fund that serves as the source of DDTSS student and postdoctoral award funding. It is used to honor outstanding abstracts presented at the Annual Meeting that demonstrate the application of modern approaches in the field of drug discovery. Dr. Pfitzer served as President of the Society of Toxicology from 1985-1986. He worked at Hoffman-LaRoche for 22 years where he was the Vice President of Toxicology and Pathology and promoted the adoption of mechanistic toxicology. Following his tenure at Roche, he served for 5 years as the President of the Research Institute for Fragrance Materials (RIFM) and it is this institution that initially created this fund by a generous contribution. While the balance of the fund remains strong, each year a greater amount is disbursed in awards than is contributed so we request that members consider donating to the fund; any contribution amount is greatly appreciated and some companies may match your personal donation to effectively double your giving.

2011 Meeting Highlights

Our DDTSS reception at the SOT Annual Meeting was reasonably well attended by our members, but we'd love to increase our attendance - although Wednesday night is often the least well attended for SS meetings; we tentatively have a Monday evening timeslot for 2012. Cindy Afshari, our 2010-2011 President presided over the meeting and gave opening and closing remarks, including the "Top 10 reasons you know you were at SOT in Washington, DC." (Craig Thomas is already sweating upholding this tradition for San

Francisco!) John Wisler presented an overview of the SOT program process and encouraged all members to submit ideas for the 2012 SOT program. Cindy Afshari presented certificates and thanks to our out-going officers: John Davis (out-going Past President), Melissa Rhodes (out-going Secretary/Treasurer), Dan Kemp (out-going Councilor), Arun Asaithambi (out-going Graduate Student Representative) and Kim Henderson (out-going Postdoctoral Representative). (Note: Dan and Kim were unable to attend and thus not in any photos.) Finally, Craig Thomas presented the top three student and postdoctoral Emil Pfitzer Student Awards. As established in 2010, GeneGo (now part of Thompson Reuters) contributed a complementary year subscription to their software tools to the top winner in each category.

2011 Emil A. Pfitzer Drug Discovery Student and Postdoctoral Fellow Competition Results

Awards were made at the 2011 Annual Meeting with funding from the Emil A. Pfitzer Endowment Fund.

Student Awards:

First Place ($1000 + GeneGo subscription)

Hariharan Swaminathan (Iowa State University). "FYN kinase activation contributes to MPTP-induced dopaminergic neurotoxicity: relevance to the pathogenesis of Parkinson's disease."

Second Place ($600)

Rachel Tanos (Penn State University). "Regulation of cholesterol biosynthetic gene expression by Ah receptor through a DNA-independent mechanism."

*Rachel is our new Graduate Student Representative.

Third Place ($300)

Jeremy Larson (University of Wisconsin-Milwaukee). "Gold nanoparticles and rat ovarian gene expression."

Postdoctoral Awards:

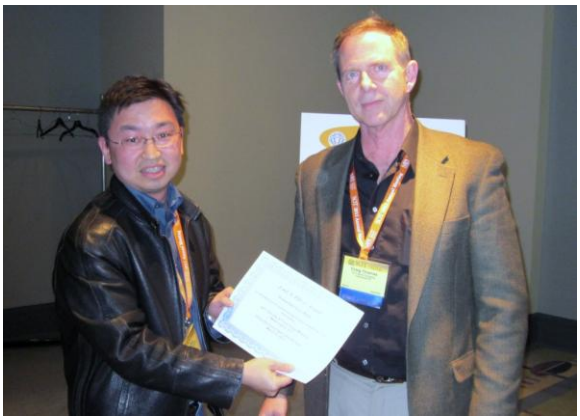
First Place ($1000 + GeneGo subscription)

Jennifer Cohen (Roche, New Jersey). "Involvement of AMPK in Sunitinib mediated cardiotoxicity in human stem cell derived cardiomyocytes."

Second Place ($ 600)

Li Zhan (University of Louisville). "Recovery of cytochrome c oxidase activity is required for dietary copper supplementation-induced regression of cardiac hypertrophy in mice."

*Li is our new Postdoctoral Representative.



Third Place ($300)

Andaleb Kholmukhamedov (Medical University of South Carolina). "Minocycline and doxycycline, but not tetracycline, decrease liver and kidney injury after hemorrhagic shock and resuscitation in mice."

Thoughts on Communication

Let's face it – everyone is busy and there is more information available on a daily or minute-by-minute basis than we can readily process. Nonetheless, the success of any organization, including the DDTSS, is predicated upon being able to access and process relevant information and to leverage the collective strengths of the organization's members. As mentioned in the President's letter, your officers intend to distribute a short survey that is intended, in part, to solicit your ideas on how we communicate amongst our membership and ensure we are maximizing member engagement and maximizing value for ourselves, the DDTSS and SOT. The officers have discussed several ideas, including the inclusion of brief write-ups of topics thought to be of interest to DDTSS members. We began this with the Summer2010 newsletter and continue it below with the contribution by **Dinah Misner** and **Mike Breider**. Another idea was the inclusion of scientific 'soundbites,' for example, similar to what one sees on a state by state basis in the USA Today newspaper.

One concrete and immediate means by which we can improve communication across our membership is *via* active use of **ToXchange** on the SOT website. We encourage each of you to access this tool (www.toxchange.org), set up your profile and select your Communities, including DDTSS. The site can be used by all to create discussion threads and the DDTSS officers can post relevant documents for information and comment. However, this tool is only useful if we all set up our profiles and commit to using it as a key communication vehicle, so please do so upon reading this newsletter. Thanks!!!

Use of Safety Information from Non-Traditional Toxicology Studies

By Dinah Misner and Michael Breider; Exploratory Toxicology, Celgene Corporation, San Diego, CA

As toxicologists supporting early discovery research, we often have limited information on toxicity of potential candidate compounds (either related to engagement of the target or off-target effects of the chemical series), until a compound has been scaled up in sufficient quantity to run short-term rodent toxicology studies. Often, such scale-up occurs late in lead optimization, sometimes not until a short-list of compounds has been identified for more extensive profiling. At such time, effects in repeat-dose rodent toxicology studies are then assessed, but when adverse effects are identified, it may be too late to adequately address such effects and make chemical modifications. Earlier assessment of the safety of a chemical template or target is therefore highly desirable and may in fact be critical to the success of a project, but making the investment in the scale-up and assessment of a tool compound(s) can be difficult to justify. To fill the gap of early toxicological data, it is possible to incorporate safety endpoints into non-toxicology studies such as efficacy and pharmacokinetic (PK) studies.

For many discovery projects, single-dose tolerability and PK is assessed prior to initiation of chronic efficacy studies (duration of which could be as short as 5 days or as long as 12 weeks). As part of this assessment, more detailed behavioral endpoints can be monitored in either rats or mice, with a consistent lexicon of clinical observations for use by PK scientists. Such an approach can provide accurate single dose tolerability data, in addition to the plasma exposures, and may also identify parameters to monitor more closely in both subsequent efficacy and toxicology studies.

During chronic efficacy studies, the addition of safety endpoints can be implemented, depending on the model used (e.g. the level of "disease" induced). The questions being asked would also depend on the potential toxicological liabilities associated with the target or to expected findings with a chemical template. These efficacy studies usually monitor pharmacokinetic/pharmacodynamic (PK/PD) relationships and blood samples are readily available for hematology and clinical chemistry assessment. For example, in chronic animal models, monitoring of clinical chemistry and hematology endpoints over time can provide insight into progression of disease, as well as highlighting treatment-related changes. In addition, a limited subset of organs may be collected at necropsy for histopathology assessment, based on presumed target organs or clinical observations made during the study. It is important to note, however, that the doses used in these efficacy studies are generally much lower than doses used in toxicology studies, and in fact may only answer questions related to on-target activity as off-target effects may not be elicited at such doses. Information regarding on-target effects, in addition to the efficacy readout, can be useful at earlier stages, particularly for novel targets where little data related to either the target or the mechanism may be available. Additionally, efficacy models often employ either diseased animals or some sort of treatment to disrupt normal physiology, and may not accurately predict compound-related toxicological changes in traditional toxicology studies. In some cases, disease is induced by genetic manipulation, altering diets or surgical interventions and may have long-term effects that confound interpretation of safety data in these models. Despite these limitations, toxicology data from efficacy studies can be used to identify trends across treatment groups, identify consistent safety issues with a compound series, or rank order compounds for additional testing.

Additionally, to enable repeat-dose rodent toxicology studies, single-dose proportionality studies are routinely conducted to assess dose-related exposure increases and tolerability. The dose levels in these studies are similar to those used in toxicology studies, thus providing the first glimpse into effects of compound administration at high doses (e.g. up to 1000 mg/kg generally), such as clinical observations, clinical chemistry, hematology, and appropriate histopathology to address a specific project-related questions.

In summary, incorporation of safety endpoints into non-traditional studies can provide valuable information earlier in a project. In order to generate meaningful data, care must be taken when selecting potential endpoints for interrogation as it is not feasible to incorporate every safety endpoint in a PK or efficacy study. Additionally, planning and coordination of these efforts across disciplines are necessary, requiring close interdepartmental collaboration. Although these safety data are not routinely used to make go/no go decisions on safety, the data have been useful in identifying safety issues early for further characterization or to prioritize compounds for scale-up and additional profiling.

SOT CCT Meetings Eligible for Seed Money and Profit Sharing

SOT Sponsors two types of meetings outside of the SOT Annual Meeting: Contemporary Concepts in Toxicology (CCT) and Non-SOT meetings. CCT meetings are one- to two-day focused, open registration, scientific meetings in contemporary and rapidly progressing areas of toxicological sciences. Non-SOT meetings are sponsored by other not-for-profit organizations and SOT will either endorse or provide sponsorship money to toxicology-related meetings.

The Society will underwrite all the liabilities of the CCT meeting with the expectation that the meeting will at least break even financially. The goal of providing $25,000 seed funds is to stimulate the creation of CCT meeting proposals.

For more information about CCT meetings, please visit the SOT Web site.

Requests for Newsletter Submissions

We are always looking for ideas and contributions for future newsletters. This can be a forum for our members to bring new ideas to our attention to elicit opinions. This can be opinion pieces or the latest research developments that impact drug safety assessment, policy changes, etc. (See the article from Misner and Breider as an example.) If you are interested in making a contribution or supplying an idea, please e-mail Donna Mendrick (donna.mendrick@fda.hhs.gov) by September 1, 2011.